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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/509,775	03/31/2000	JUN FUJITA	053466/0277	9739

22428 7590 09/21/2004

FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/509,775	FUJITA, JUN	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2004 and 04 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 5-35* is/are pending in the application.

4a) Of the above claim(s) *6-15 and 18-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,16,17 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Exhibit A*.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 4, 2004 has been entered. Claims 1, 16, and 17 are amended.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This Office action contains new grounds of rejection.

Election/Restrictions

Claims 6-15, and 18-34 are withdrawn for reason of record from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

Claims 1, and 5-35 are pending. Claims 1, 5, 16,17, and 35 are examined on merits.

Claim Objections, Withdrawn

The objection is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 112

The rejection of the claims under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is **withdrawn** in view of the amendment.

Claim 1 **remains rejected** and claims 5, 16, 17, and 35 are **newly rejected** under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1 is drawn to a polypeptide consisting of amino acid #14 to #226 of SEQ ID NO:2 and having biological activity of gankyrin, claims 5, and 35 are drawn to polypeptides encoded by nucleic acid molecules hybridizing to SEQ ID NO:1, and claims 16, and 17 are drawn to a signal added polypeptide consisting of amino acid #14 to #226 of SEQ ID NO:2 and having biological activity of gankyrin, wherein the signal does not come from the N-terminal 13 amino acids of instant SEQ ID NO:2.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Applicant argues that the invention of claim 1 provides a polypeptide consisting of an amino acid sequence from Ala at position 14 to Gly at position 226 of SEQ ID NO: 2 and haying biological activity of gankyrin. Indeed, the Applicant has discovered that an amino acid sequence from Ala at position 14 to Gly at position 226 of SEQ ID NO: 2

has a biological activity of gankyrin. As acknowledged by the Examiner, the specification discloses several biological activities of gankyrin, enhancement of colony formation, tumorigenic properties and suppression of apoptosis induction. See Example 4. The specification also discloses methods of assaying biological activities of gankyrin. The Examiner provides no objective reason and certainly no documentary evidence to support that the claim is not enabled. These arguments have been fully considered but found unpersuasive for the reason of record.

As stated at pages 3-5 of the Office action mailed on 11/06/2003, the specification at Example 4 (pages 55-58) discloses that the various biological activities of gankyrin is the characteristics of the SEQ ID NO:2, which is encoded by the 678-bp cDNA isolated in Example 1 (pages 45-48). Unlike applicant's assertion, the specification does not disclose that a polypeptide consisting of an amino acid sequence from amino acid position #14 to 226 of instant SEQ ID NO:2 has the biological activity of gankyrin.

As stated before, protein chemistry is unpredictable in the current state of art. For example, Wang, J. et al., of record (2000 J. Biol. Chem. 275 (1): 507-513) provide evidence that even a single amino acid change in a protein converts in vivo activity in unpredictable way (see Table 1). Bowie et al., of record (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein

structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al., of record (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Lazar et al., of record (Molecular and Cellular Biology, 1988, 8:1247-1252) teach that conservative substitutions in a protein do not lead to retaining biological activity of a protein. Lazar et al teach that transforming growth factor alpha, replacement of aspartic acid at position 47 with non-conservative residue alanine did not affect biological activity while replacement with a conservative residue, glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution or "conservative" amino acid substitution in a protein will often dramatically affect the biological activity and characteristics of a protein.

Further, Higashitsuji et al., (2000, Nature Medicine, vol. 6, pages 96-99) teach at Fig. 2, that the N-terminal amino acid of the gankyrin polypeptide is required in order to

have the gankyrin activity. Note specially Fig. C. Also note that the instant inventor is one of the authors of the publication.

Applicant is invited to present scientific evidence that a polypeptide consisting of an amino acid sequence from amino acid position #14 to 226 of instant SEQ ID NO:2 indeed has the biological activity of gankyrin in order to obviate the rejection of claim 1 under enablement.

Further, for claims 16, and 17, drawn to the polypeptide of claim 1 with an art-known heterologous signal sequence attached, Hori et al., teach at page 113 that the protein called p28, identical to instant SEQ ID NO:2 (see Exhibit A) is a subunit of the intracellular 26S proteasome complex. It appears that the biological activity of gankyrin appears to be the result of the protein being present in cytosol, not in any other compartment of the cell. Neither the specification nor art teaches that the protein should be directed to different compartment of the cell with a signal sequence. Further, as stated above, Higashitsuji et al., teach that the N-terminal amino acid sequence is necessary for gankyrin activity. It appears that instant SEQ ID NO:2 with intact N-terminal amino acids is required fro the gankyrin activity of the polypeptide as disclosed in Higashitsuji et al. Since instant SEQ ID NO:2 is an intracellular protein as taught by Hori et al., it is not clear whether a signal sequence (such as directing a protein to membrane) added polypeptide consisting of amino acid #14 to #226 of SEQ ID NO:2 would have a biological activity of gankyrin. Both Higashitsuji et al., and Hori et al., appear to teach that the biological activity of gankyrin protein comes from the protein

being an intracellular protein, not a membrane protein, or a protein of any other cellular compartment that requires a signal sequence.

As for claims 5, and 35, the specification teaches that instant SEQ ID NO:1 is a human cDNA i.e. the sense strand encoding SEQ ID NO:2 protein. Likewise, Hori et al., (08/17/1998, Gene, vol. 216, pages 113-122) teach at page 113 that the protein called p28, identical to instant SEQ ID NO:2 (see Exhibit A) is encoded by cDNA structure that is identical to the protein coding sequence of instant SEQ ID NO:1. This indicates that the complementary strand or similar nucleic acid structure that would hybridize to instant SEQ ID NO:1 might not encode any protein, let alone encoding protein that has gankyrin activity. Neither the specification nor any art of record teaches that the complementary strand hybridizing to instant SEQ ID NO:1 encodes any protein. The specification does not teach how to make a protein having the biological properties of gankyrin using the recited hybridizing molecules to instant SEQ ID NO:1.

Considering the unpredictable state of art, limited guidance, no examples in the specification how to make (for the polypeptide in claims 5, and 35) and use the instantly claimed invention, broad breath of the claims, it is concluded that undue experimentation is required to practice the invention.

Claim Rejections - 35 USC § 102, Withdrawn

The rejection of claims 5 and 35 under 35 U.S.C. 102(b) as being anticipated by Kato et al (IDS, JP 9-75085, published 25 March 1997) is withdrawn because the claims are drawn to polypeptide encoded by a DNA molecule hybridizing to SEQ ID NO:1, which is the sense strand encoding instant SEQ ID NO:2. The hybridizing DNA

molecule should look similar to the complementary to SEQ ID NO:1. However, neither the specification nor any art of record teaches a complementary to instant SEQ ID NO:1 encodes any protein. See the written description rejection below.

Claim Rejections - 35 USC § 103, Withdrawn

The rejection of claims 16 and 17 under 35 U.S.C. 103(a) as being unpatentable over Kato (IDS, JP 9-75085, published 25 March 1997) as applied to claims 5 and 35 above, and further in view of Zhang et al (1995, a copy provided in the previous Office action) and Jamsa et al (1995, a copy provided in the previous Office action) is withdrawn.

The Following Are New Grounds of Rejection

Claim Rejections - 35 USC § 112

Claims 5, and 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has two parts, i.e. a new matter rejection and a written description rejection.

The applicable standard for the written description requirement can be found: MPEP 2163; University of California v. Eli Lilly, 43 USPQ2d 1398 at 1407; PTO Written Description Guidelines; Enzo Biochem Inc. v. Gen-Prove Inc., 63 USPQ2d 1609; Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111; and University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC 2004).

First, claims 5, and 35 are rejected for failing to provide failing to provide the written description requirement because the Office interprets that claims 5, and 35 are drawn to genus of polypeptides encoded by nucleic acid molecules hybridizing to SEQ ID NO:1.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

The specification teaches that instant SEQ ID NO:1 is the sense strand encoding instant SEQ ID NO:2. Thus, the complementary strand would hybridizes to instant SEQ ID NO:1, as applicant states at page 11 of the response filed on 7/6/2004. Also note at pages 503-505 of THE ENCYCLOPEDIA OF MOLECULEAR BIOLOGY (1994) attached with the response filed 7/6/2004, especially at page 503, left column under the heading "Hybridization" that discloses "The two polynucleotide strands are held together in an antiparallel configuration by hydrogen bonding between bases G and C and A and T." Thus, SEQ ID NO:1 would not able to hybridize to SEQ ID NO:1 because hybridization would not occur since SEQ ID NO:1: SEQ ID NO:1 pair lack hydrogen bonding partners. Careful examination of the instant claims 5, and 35 indicate that the claimed polypeptides are encoded by the complementary strand to instant SEQ ID

NO:2, which encodes a human protein. However, the specification does not teach the structure of a protein encoded the complementary of instant SEQ ID NO:1.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of proteins, given that the specification has only described SEQ ID NO:1 encodes SEQ ID NO:2.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey C Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, PH.D.
Examiner
Art Unit 1642

EXHIBIT 11

Page 1 of 2

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Copyright (c) 1993-2000 Compugen Ltd.

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sp_plant:Q9ZQ79	+	338.00	541.58	2.5e-22	247	Q9zq79 arabidopsis thaliana (mc
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DT 01-NOV-1998 (TrEMBLrel. 08, Last sequence update)
DT 01-MAR-2001 (TrEMBLrel. 16, Last annotation update)
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OC Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
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RX MEDLINE=98382579; PubMed=9714768;
RA Hori T., Kato S., Saeki M., DeMartino G.N., Slaughter C.A.,
RA Takeuchi J., Toh-E A., Tanaka K.;
RT "cDNA cloning and functional analysis of p28 (Nas6p) and p40.5
RT (Nas7p), two novel regulatory subunits of the 26S proteasome.";
RL Gene 216:113-122(1998).
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RL Submitted (JAN-1999) to the EMBL/GenBank/DDBJ databases.
RN [3]
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RA Higashitsuji H., Fujita J.;
RT "Enhanced expression of a novel tumour marker in the human
RT hepatomas.";
RL Submitted (JAN-1996) to the EMBL/GenBank/DDBJ databases.
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DR EMBL; AL031177; CAA20117.1; -.
DR EMBL; D83197; BAA34594.1; -.
DR HSSP; P42773; 1IHB.
DR InterPro; IPR002110; -.
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    197 CTAGAACTGACCAGGACAGCAGAACTGCATTGCACTGGGCATGCTCAGCT 246
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Page 2 of 2

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DT   01-MAY-1999 (TrEMBLrel. 10, Created)
DT   01-MAY-1999 (TrEMBLrel. 10, Last sequence update)
DT   01-MAR-2001 (TrEMBLrel. 16, Last annotation update)
DE   GANKYRIN HOMOLOGUE.
OS   Rattus norvegicus (Rat).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Rattus.
OX   NCBI_TaxID=10116;
RN   [1]
RP   SEQUENCE FROM N.A.
RC   TISSUE=PLACENTA;
RA   Higashitsuji H., Fujita J.;
RT   "Cloning of rat gankyrin homologue containing ankyrin repeats.";
RL   Submitted (JAN-1999) to the EMBL/GenBank/DDBJ databases.
DR   EMBL; AB022014; BAA36954.1; -.
DR   HSSP; P42773; 1IHB.
DR   InterPro; IPR002110; -.
DR   Pfam; PF00023; ank; 5.
DR   PROSITE; PS50088; ANK_REPEAT; 5.
DR   PROSITE; PS50297; ANK_REP_REGION; 1.
DR   SMART; SM00248; ANK; 1.
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alignment_scores:
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DT   01-MAY-1999 (TrEMBLrel. 10, Created)
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